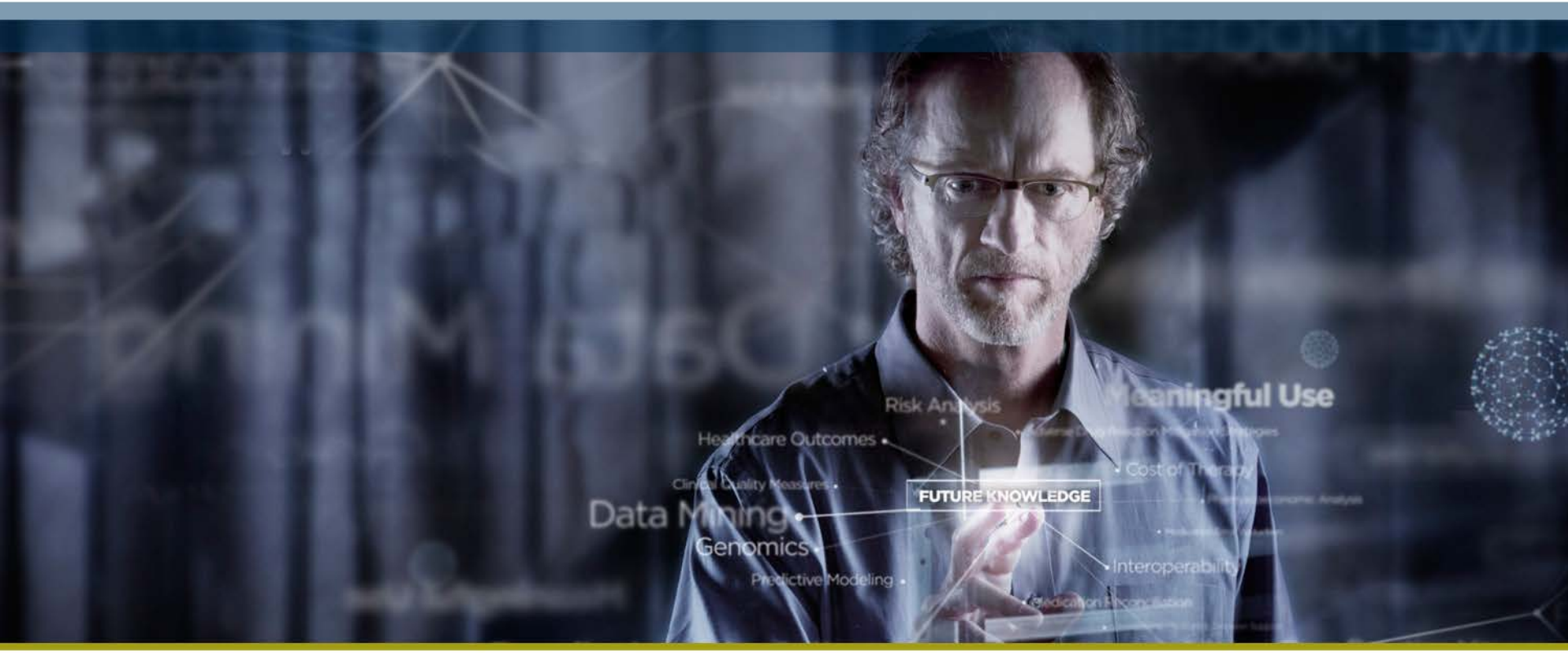
First Databank



Strategies for Improving Drug Interaction Alerts for Clinical Decision Support (CDS)

Karl Matuszewski, MS, PharmD, VP Clinical Editorial, First Databank

FDA Advisory Committee Meeting, September 25, 2013

FDB (First Databank)

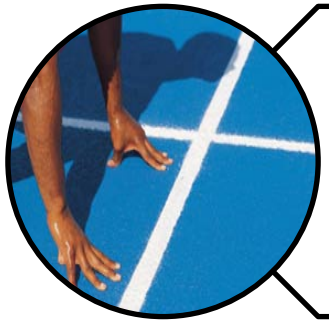
- FDB is a subsidiary of Hearst Corporation and the leading provider of drug knowledge that helps healthcare professionals make precise medication-related decisions.

- FDB creates and maintains widely used drug knowledge, software for drug knowledge integration, and drug reference products. The firm has partnered with other information system developers to make drug information useful within the workflow for a wide range of healthcare professionals.

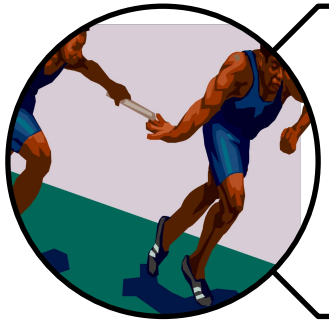
- FDB's drug knowledge supports pharmacy dispensing, formulary management, drug pricing analysis, medical insurance claims processing, computerized prescriber order entry (CPOE), electronic health/medical records (EHR/EMR), electronic prescribing, and electronic medication administration records (EMAR) systems.

- FDB influences the incidence of medication errors and adverse events associated with prescription drugs that have an impact on healthcare costs and the overall quality of patient care.

AGENDA



Medication CDS lives in a complicated realm, but editorial policies supporting evidence-based content is a focus for FDB



Three pronged approach to alert fatigue has FDB moving the mark clinically

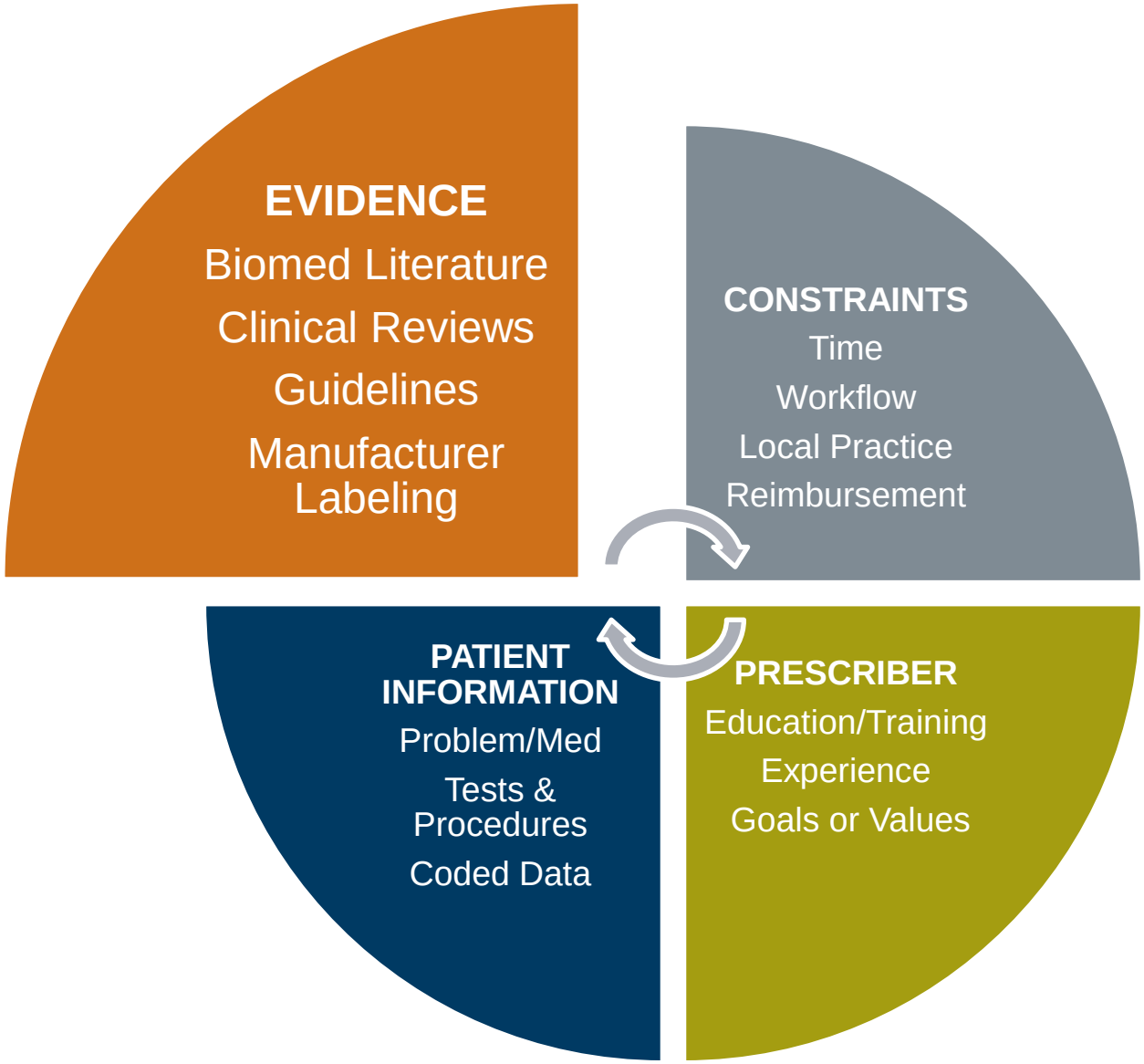
Content with additional drug or patient parameters and filters including med cycle focus

FDB FOUNDATIONAL APPROACH

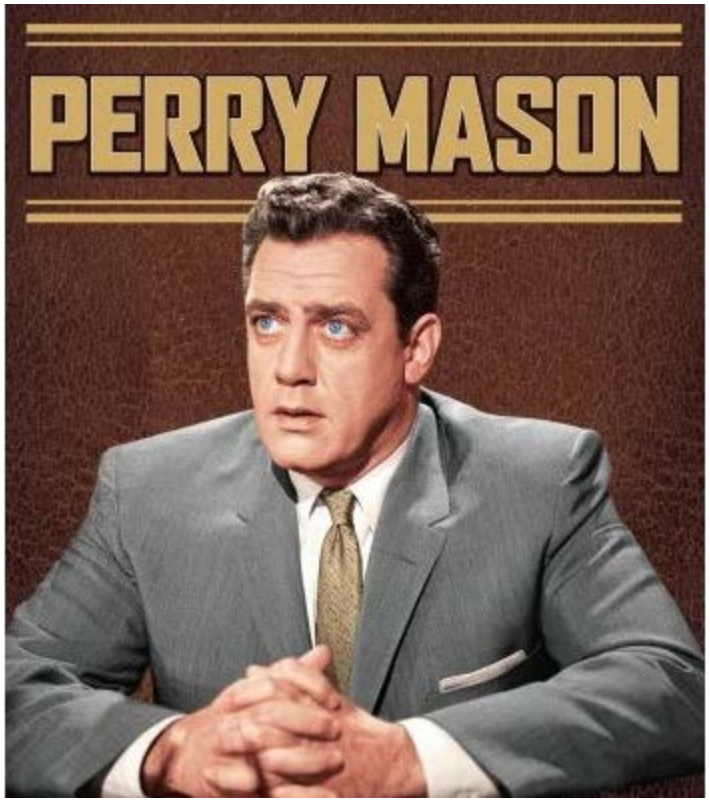
Surveillance for Evidence

CDS Lives in this Realm

A Multitude of Changing Factors in Clinical Decision Making



EVIDENCE is in the Eye of the Beholder!



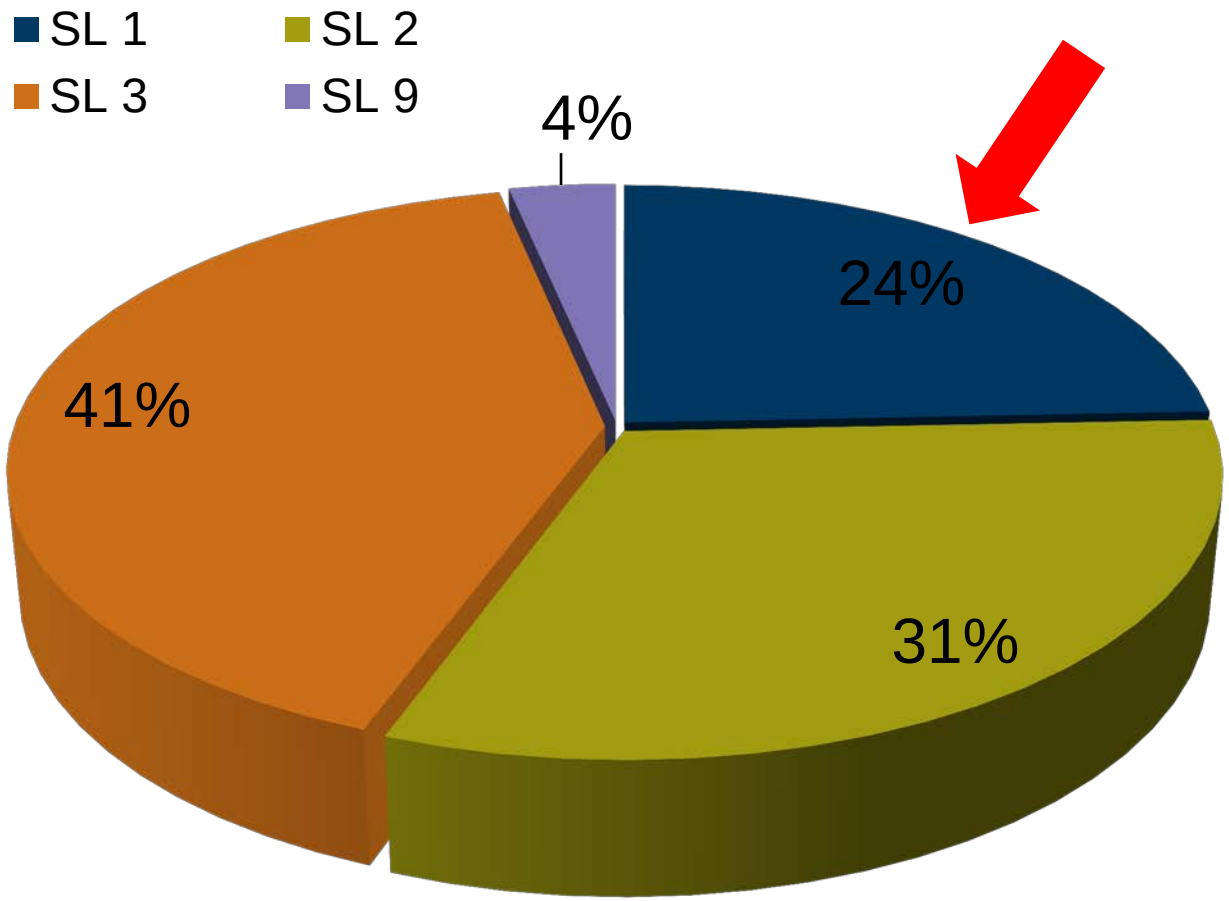
Drug Knowledgebase Maintenance/Data Curation

- *Content creation responsibilities*
  - Experienced Clinical Pharmacists with honed judgment, expert review prn
  - Understanding of health system applications and workflow
- *Capture drug information*
  - “trigger events” – tracking systems
  - Accountable assessment plan
- *Comprehensive evidence review*
  - timely review enforced
  - compliance with Editorial Policies
  - consistent with quality controls
  - new knowledge sources acquired (drug metabolism literature database)

Evaluations of Drug Interactions (EDI)

- Loose-leaf reference started in 1984, bimonthly updates
- 18 chapters, 2000 pages, based on major therapeutic classes
- 14 member external advisory board
- Sections: Title of DDI, summary, related drugs, mechanism, recommendations, references, tables

FDB DDI Severity Level Breakdown, N ~ 1600



Alert Fatigue or Knowledge Denial?

New antiepileptic drug safety information is not transmitted systematically and accepted by U.S. neurologists ☆

Sarah G. Bella, Martha Matsumotoa, Susan J. Shawb, Jason Brandtc, Gregory L. Kraussa,
a Johns Hopkins University, Department of Neurology, 600 N. Wolfe St., Meyer 2-147, Baltimore, MD 21287, USA
b University of Southern California, Keck School of Medicine, Department of Neurology, Rancho Los Amigo National Rehabilitation Center, 7601 E. Imperial Highway, HB 145, Downey, CA 90242, USA
c Johns Hopkins University, Division of Medical Psychology, 600 N. Wolfe St., Meyer 218, Baltimore, MD 21287, USA

Highlights

- Survey US neurologists' knowledge of FDA safety warnings for AEDs.
- Respondents received safety information non-systematically from multiple sources.
- One-fifth (20%) did not recognize recently identified, serious AED safety risks (e.g., suicidality, birth defects, side effects).
- FDA-recommended pharmacogenomic screening for carbamazepine was not carried out.
- Neurologists would prefer receiving FDA safety updates via specialty organizations.

Pace of “official” Change Notice

Year	FDA MedWatch Alerts	Drug Safety Withdrawals
2009	122	0
2010	140	0
2011	136	1
2012	169	3
2013 (YTD)	138	1

Making Headway with Alert Management

Fine-tune Existing Content

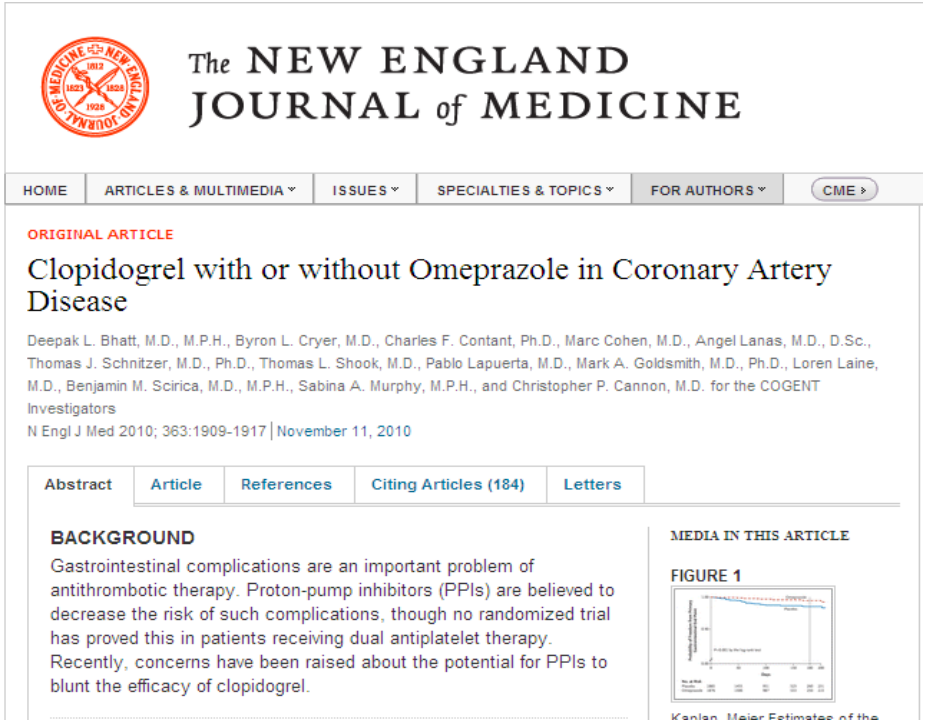
Create Additional Parameters and Filters

Local Customization

New, Highly-Specific Decision Support

Drug-Drug Interactions: FDB Making Hard Choices

- Over 75 drug interaction pairs are strength-breakouts
- Drug interaction applications can take advantage of route breakouts (e.g., topicals)
- Limiting class effects - clopidogrel/proton pump inhibitors
  - esomeprazole (Nexium) & omeprazole (Prilosec), Severity Level=2
  - lansoprazole (Prevacid), pantoprazole (Protonix) changed to Severity Level=3



The NEW ENGLAND JOURNAL of MEDICINE

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ORIGINAL ARTICLE

Clopidogrel with or without Omeprazole in Coronary Artery Disease

Deepak L. Bhatt, M.D., M.P.H., Byron L. Cryer, M.D., Charles F. Contant, Ph.D., Marc Cohen, M.D., Angel Lanas, M.D., D.Sc., Thomas J. Schnitzer, M.D., Ph.D., Thomas L. Shook, M.D., Pablo Lapuerta, M.D., Mark A. Goldsmith, M.D., Ph.D., Loren Laine, M.D., Benjamin M. Scirica, M.D., M.P.H., Sabina A. Murphy, M.P.H., and Christopher P. Cannon, M.D. for the COGENT Investigators

N Engl J Med 2010; 363:1909-1917 | November 11, 2010

Abstract | Article | References | Citing Articles (184) | Letters

BACKGROUND

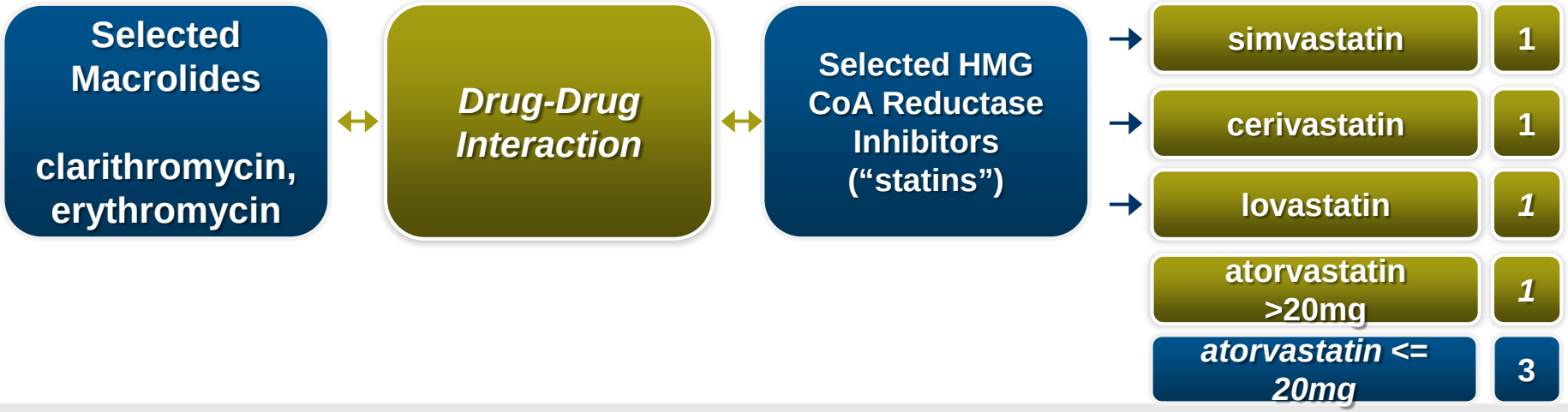
Gastrointestinal complications are an important problem of antithrombotic therapy. Proton-pump inhibitors (PPIs) are believed to decrease the risk of such complications, though no randomized trial has proved this in patients receiving dual antiplatelet therapy. Recently, concerns have been raised about the potential for PPIs to blunt the efficacy of clopidogrel.

MEDIA IN THIS ARTICLE

FIGURE 1

Fine-Tuned Content: Drug-Drug Interactions

Breakout Ingredients & Adjusting Severity Level based on agent-level evidence

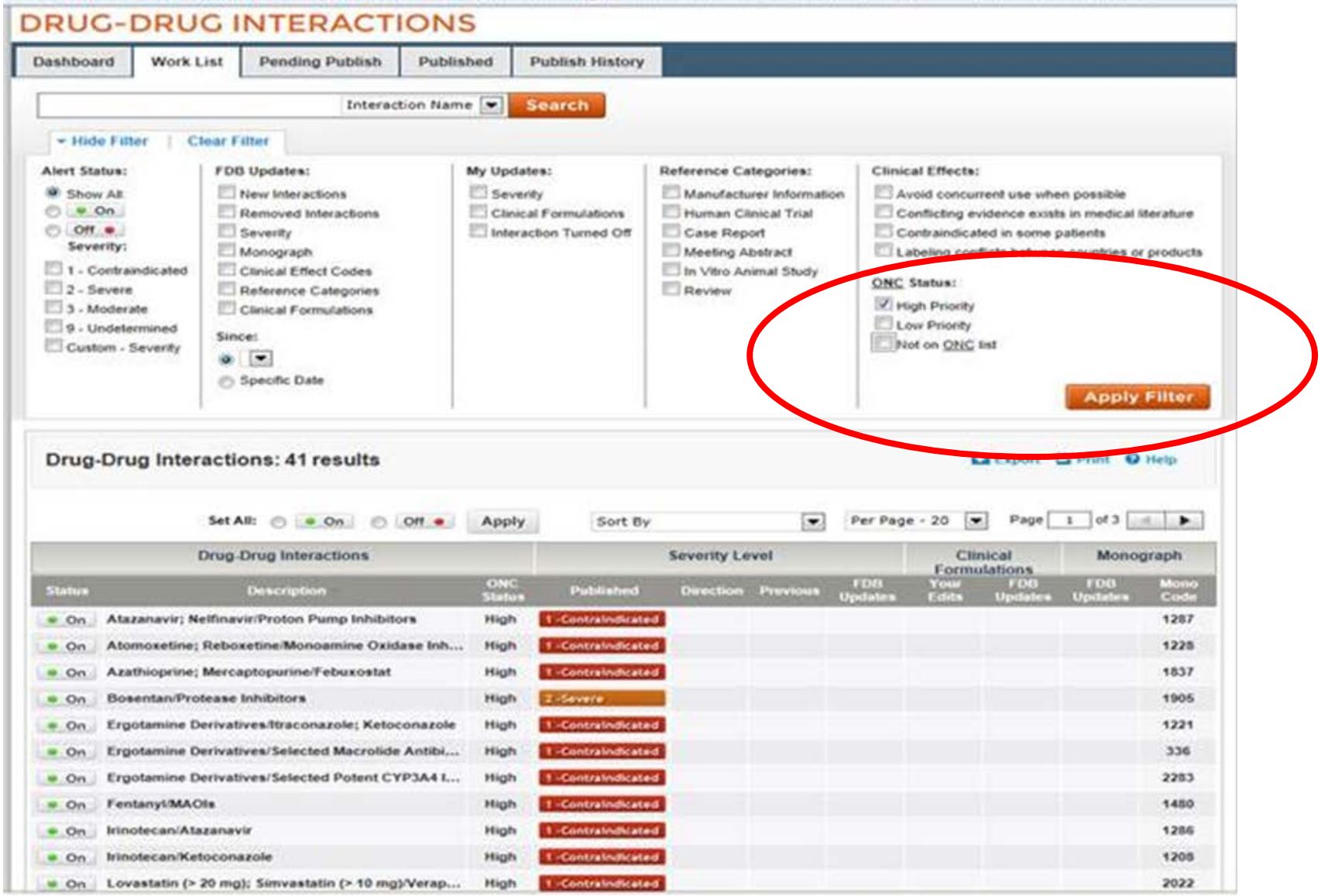


Bottom Line: Fewer Inappropriate Alerts

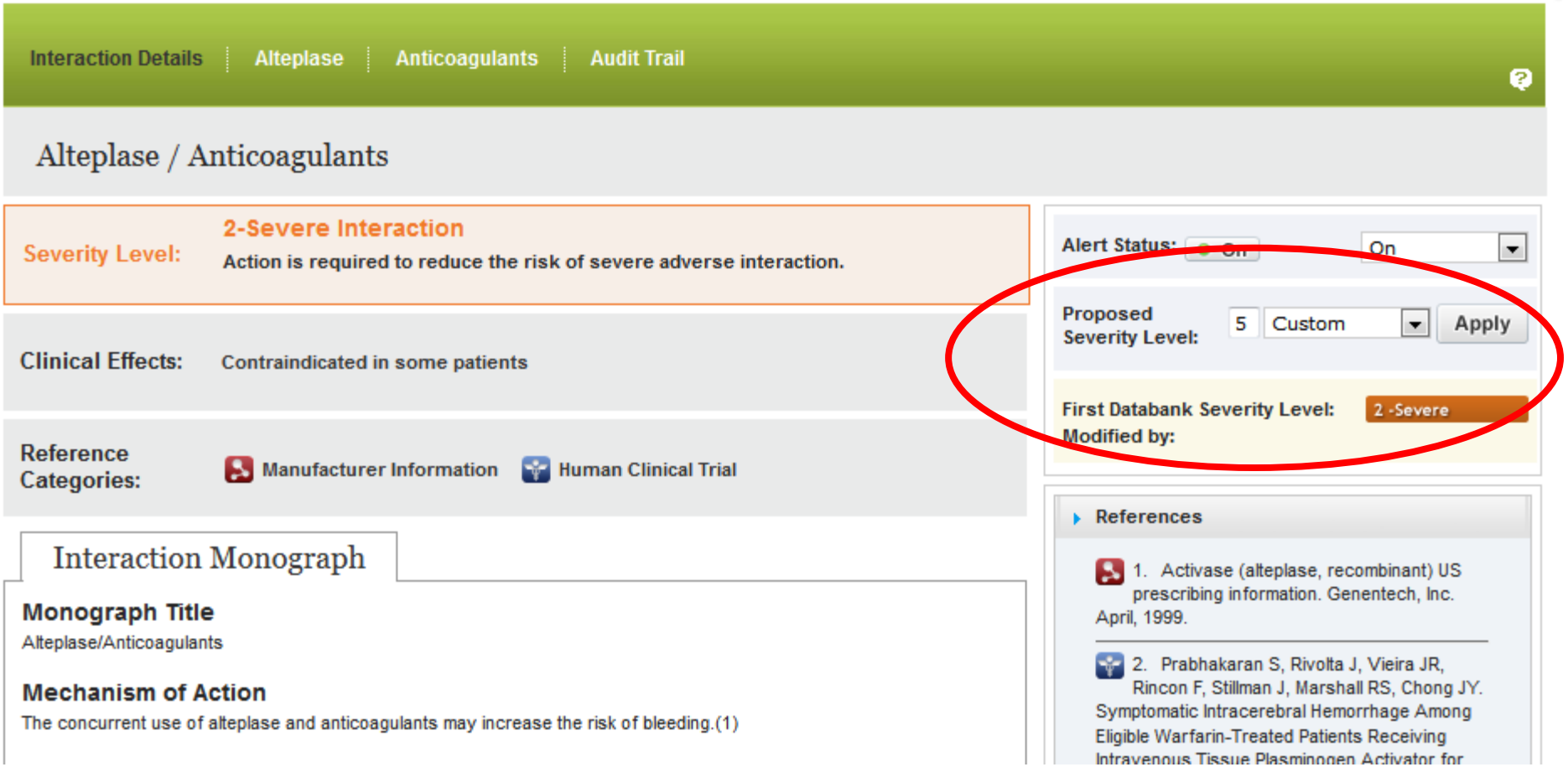
FDB's AlertSpace™

Allowing for Local Customization

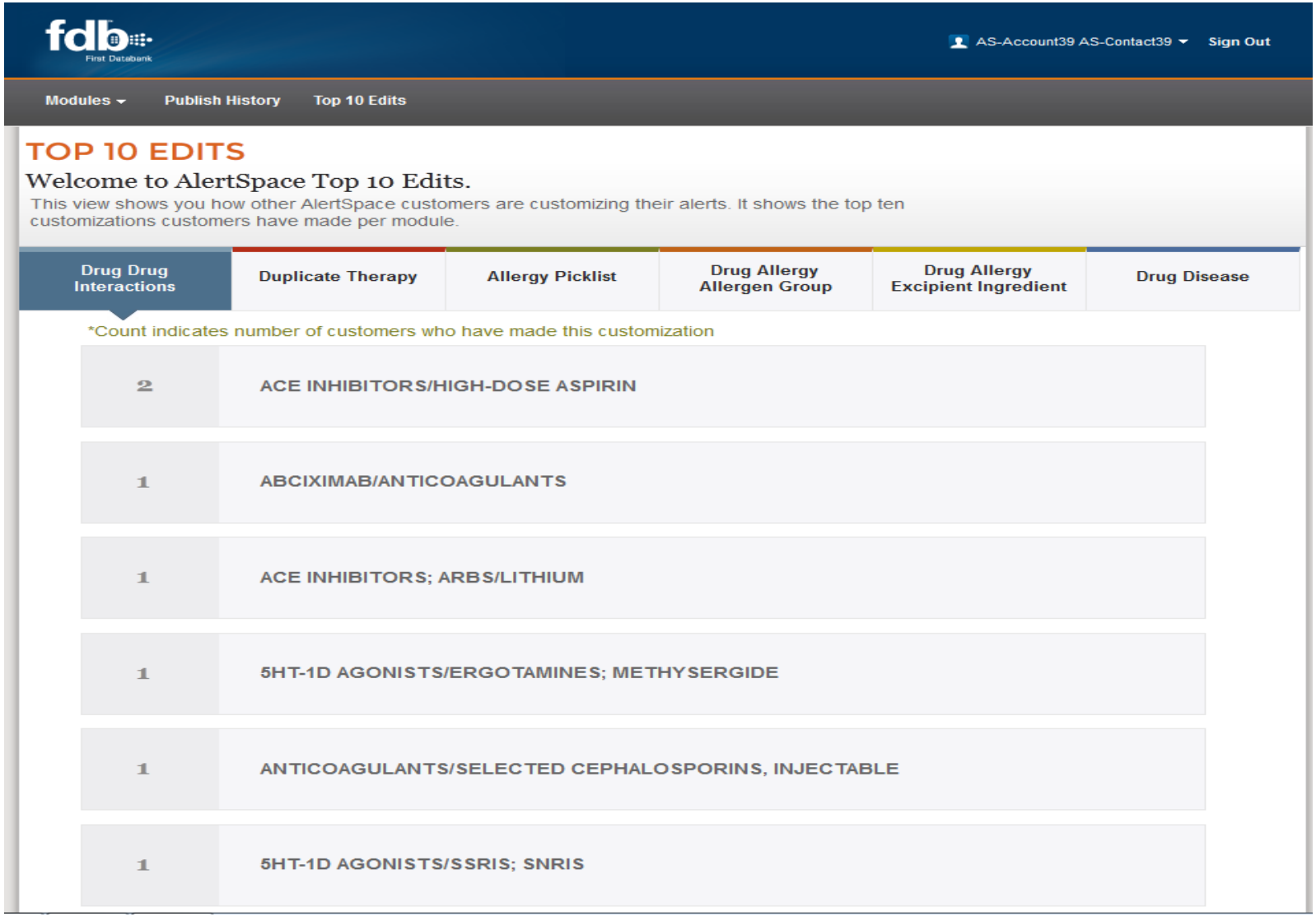
Implementation of Authoritative DDI Subsets



CUSTOM SEVERITY LEVEL- Targeted Alerts



Crowd Source- Potential Top Customizations



NEW FDB CAPABILITY
Customer Alert Reports Feedback Loop

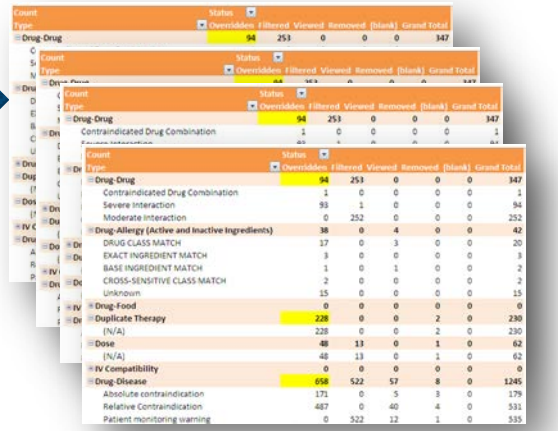
Making Headway with Alert Management

EVIDENCE- Allows Fine-tuning of Existing Content

Create Additional Parameters and Filters

Local Customization

Aggregated Alert Reports



New, Highly-Specific Decision Support

Essential Alert Report Feedback Loop to Prioritize Evidence Review

Count	Status					
Type	Overridden	Filtered	Viewed	Removed	(blank)	Grand Total
Drug-Drug	**94**	**253**	**0**	**0**	**0**	**347**
Contraindicated Drug Combination	1	0	0	0	0	1
Severe Interaction	93	1	0	0	0	94
Moderate Interaction	0	252	0	0	0	252
Drug-Allergy (Active and Inactive Ingredients)	**38**	**0**	**4**	**0**	**0**	**42**
DRUG CLASS MATCH	17	0	3	0	0	20
EXACT INGREDIENT MATCH	3	0	0	0	0	3
BASE INGREDIENT MATCH	1	0	1	0	0	2
CROSS-SENSITIVE CLASS MATCH	2	0	0	0	0	2
Unknown	15	0	0	0	0	15
Drug-Food	**0**	**0**	**0**	**0**	**0**	**0**
Duplicate Therapy	**228**	**0**	**0**	**2**	**0**	**230**
(N/A)	228	0	0	2	0	230
Dose	**48**	**13**	**0**	**1**	**0**	**62**
(N/A)	48	13	0	1	0	62
IV Compatibility	**0**	**0**	**0**	**0**	**0**	**0**
Drug-Disease	**658**	**522**	**57**	**8**	**0**	**1245**
Absolute contraindication	171	0	5	3	0	179
Relative Contraindication	487	0	40	4	0	531
Patient monitoring warning	0	522	12	1	0	535

Creating Additional Parameters for DDI

- Patient
  - New exposure (vs. continued therapy)
  - Normal lab parameters (e.g., K+, INR)
  - # MDs ordering meds
  - Service location (e.g., clinic vs. ICU)
  - Co-morbidities (e.g., renal/hepatic deficits)
  - Pharmacogenomics (slow/fast metabolizers)
- Physician
  - Specialty (e.g., anesthesiology vs. family medicine)
  - Role (e.g., hospitalist vs. intern)
- Drug
  - Probability (rare vs. common) → % occurrence
  - Severity (mild thru severe) → o, /, x (use of standard symbols?)

Implementation for DDI screening Factors

- Who is looking and or acting on alerts?
  - Prescribing vs. dispensing vs. administering
- What other background CDS (implemented)
  - Duplicate therapy
  - Side effects
  - Drug-disease contraindications/precautions
- The user interface (design)
  - Recall and ignore (i.e., I already approved this combo)
  - Symbolic coding (e.g., green, yellow, red or icons)
  - Bundled or prioritized alerts (vs. long list strings)
  - Screen size viewing (32” vs mobile)
  - Audio alerts? Offering alternatives? Ordering labs/monitoring?

PI Issues for Drug Interactions

- Labeling mismatches between 2 drugs
- Label inconsistencies
- Imprecise label narrative
- Outdated labels
- Broad class effect statements

Label Inconsistencies Ex. - Xenazine (9/12)

- The Highlights section states “QTc prolongation. Do not prescribe in combination with other drugs that prolong QTc. (5.11, 7.5, 7.6, 12.2).”

- Section 5.11 states “The use of XENAZINE should be avoided in combination with other drugs that are known to prolong QTc, including antipsychotic medications (e.g., chlorpromazine, haloperidol, thioridazine, ziprasidone), antibiotics (e.g., moxifloxacin), Class 1A (e.g., quinidine, procainamide), and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications or any other medications known to prolong the QTc interval *[see Drug Interactions (7.5, 7.6) and Use in Specific Populations (8.9)].”*

- Section 7.5 states “Since XENAZINE causes a small increase in QTc prolongation (about 8 msec), the concomitant use with other drugs that are known to cause QTc prolongation should be avoided including antipsychotic medications (e.g., chlorpromazine, haloperidol, thioridazine, ziprasidone), antibiotics (e.g., moxifloxacin), Class 1A (e.g., quinidine,procainamide), and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications or any other medications known to prolong the QTc interval.”

- Section 7.6 states “Adverse reactions associated with XENAZINE, such as QTc prolongation, NMS, and extrapyramidal disorders, may be exaggerated by concomitant use of dopamine antagonists, including antipsychotics (e.g., chlorpromazine, haloperidol, olanzapine, risperidone, thioridazine, ziprasidone) *[see Warnings and Precautions (5.5, 5.9, 5.11, 5.12) and Drug Interactions (7.5)].”*

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Label and Approval History

Drug Name(s)	XENAZINE
FDA Application No.	(NDA) 021894
Active Ingredient(s)	TETRABENAZINE
Company	VALEANT BERMUDA

Go to Approval History

Label Information

What information does a label include?
Note: Not all labels are available in electronic format from FDA.

The latest approved label (approved 08/02/2013) is *not available* on this site for XENAZINE, NDA no. 021894

View the label approved on 07/06/2011 (PDF)

To see if other previously-approved labels are available on this site, go to the "Approval History" section of this page.
Older labels are for historical information only and should not be used for clinical purposes.

Approval History
NDA 021894

Note: Not all reviews are available in electronic format from FDA.
Older labels are for historical information only, and should not be used for clinical purposes.
Approval dates can only be verified from 1984 to the present.

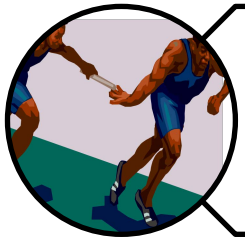
Click on a column header to re-sort the table:

Download data

Action Date	Supplement Number	Approval Type	Letters, Reviews, Labels, Patient Package Insert	Note
08/02/2013	009	Labeling Revision	Letter (PDF)	Label is not available on this site.
08/17/2012	007	Labeling Revision	Letter (PDF)	Label is not available on this site.
07/06/2011	004	Labeling Revision	Label (PDF) Letter (PDF)	
05/04/2011	005	Labeling Revision	Label (PDF) Letter (PDF)	
12/01/2009	002	Labeling Revision	Letter (PDF)	Label is not available on this site.

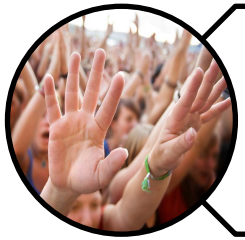
Summary

Medication Alerts live in a complicated realm, but evidence-based content is a focus for FDB



FDB's three pronged approach to alert fatigue has evolved, and continues to push the mark clinically

Evolving evidence review sources and strategies needed, along with new module tools/tactics



THANK YOU – Questions?